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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/640,636	08/17/00	LEWIN	D 15966-560 (CU

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EXAMINER	
SPIEGLER, A	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 06/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/640,636	LEWIN ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *2-4, 13-14, 19-20, and 22-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-12, 15-18, 21, and 54-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18) ☒ Interview Summary (PTO-413) Paper No(s). *14* .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. This action is in response to Paper No. 12, filed on 5/22/01. Currently claims 1-56 are pending, Group I (claims 1, 5-12, 15-18, 21, and 54-56, and SEQ ID NO: 1) have been examined on the merits, as being drawn to an elected invention. Claims 2-4, 13-14, 19-20, and 22-53 have been withdrawn from consideration, as being drawn to a non-elected invention. With respect to newly amended claims 47-51, the claims are drawn to methods using a polypeptide, whereas the claims of Group I are drawn to methods using a nucleic acid (i.e. two patentably distinct methods), and therefore, have not been examined on the merits, as drawn to a non-elected invention. Applicants are required to amend the claims to the elected invention (i.e. claims should be amended to recite SEQ ID NO: 1).

2. Applicant's election with traverse of Group I (claims 1-12, 15-18, 21, and 54-56, and SEQ ID NO: 1) in Paper No. 12 is acknowledged. The traversal is on the grounds that the simple enumeration of sequences is not grounds for restriction. Applicants present two nucleic acid sequences (SEQ ID NOS: 1 and 3) and four polypeptide sequences (SEQ ID NOS: 2 and 4-6). Applicants submit that these sequences are related, where as SEQ ID NO: 1 encodes the polypeptides of SEQ ID NOS: 2 and 6, and SEQ ID NO: 3 encodes polypeptides of SEQ ID NO: 4 and 5. Finally, applicants argue that the inclusion of the sequences in the application is necessary to make and carry out the invention, as claim 4 is drawn to the method comprising the expression of 25 or more of the nucleic acid sequences (pg. 4).

This traversal has been fully considered and thoroughly reviewed, but is deemed not persuasive for several reasons. As applicants point out, MPEP 803.04 suggests that "the Office

allows applicants up to 10 independent sequences" per application without restriction. In the present case, 2 independent and distinct nucleic acid sequences are used in the claimed method (i.e. SEQ ID NOS: 1 and 3). SEQ ID NO: 1 is derived from mouse chromosome 5 at an estimated 51cM offset from the centromere (pg. 9), whereas SEQ ID NO: 3 has 95% identity to an EST from an endometrium adenocarcinoma cell line and is 82% identical and 89% similar to pufferfish sequence CNS03HI5 (pg. 10). Clearly, these sequences are independent and distinct from each other, and furthermore, would require a search burden on the examiner. Thus, restriction is deemed proper in light of MPEP 803.04. In addition, the polypeptides of SEQ ID NOS: 2 and 6, and 4 and 5, are separate and distinct as said polypeptides are not used in the nucleic acid based methods and products of Group I. These two inventions (i.e. the polypeptides of SEQ ID NOS: 2 and 4-6, and the nucleic acid-based methods and products of Group I) have different structures and functions, and would require searching separate and non-overlapping areas, which would constitute an undue search burden on the examiner if not restricted. With respect to applicants argument that to assess the hematopoietic status of a subject, the method comprises the expression of 25 or more of the nucleic acid sequences, applicants are reminded that each of these nucleic acid sequences are independent and distinct, and therefore, are subject to restriction. A search of the distinct inventions would not be co-extensive as evidenced by the requirement for searching different keywords and nucleic acid and amino acid sequences and by the different classification of each invention. Therefore, an undue search burden would be required to examine each of the claimed inventions. Accordingly, the requirement is still deemed proper and is therefore made FINAL.

Specification

3. The disclosure is objected to because of the following informalities:

A) Page 4, , ln. 8, recites "Nature Biotechnology 17:198-803", which should be amended to recite the proper page number of the reference.

B) Page 9, ln. 22, recites "HEM1", which should be amended to "HEMA1".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 5-12, 15 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to methods of assessing hematopoietic status in a subject, comprising, providing a test cell population from the subject, wherein at least one cell in the test cell population is capable of expressing SEQ ID NO: 1, measuring the expression of SEQ ID NO: 1, in said test cell population, and comparing the expression of SEQ ID NO: 1, in the test cell population to the expression of a nucleic acid, in a reference cell population comprising at least one cell whose hematopoietic status is known, thereby indicating hematopoietic status in the subject. The claims are further drawn to methods of diagnosing or determining the susceptibility to a hematopoietic disorder in a subject and methods of assessing the efficacy of a

treatment of a hematopoietic disorder in a subject, by identifying a difference in expression levels of SEQ ID NO: 1, if present, in a test cell population and a reference cell population.

The specification teaches SEQ ID NO: 1 is localized on mouse chromosome 5 in an estimated position to be 51 cM offset from the centromere (pg. 9, ln. 17-18), and in northern and PCR analyses demonstrated a high level of Expression in the adult lung, 10.5 day old yolk sac and in AGM regions of 10.5 day old mice (pg. 9, ln. 20-21). Furthermore, the specification teaches that the polypeptide encoded by SEQ ID NO: 1 had homology to several chemokines of the CXC (alpha) family (pg. 9, ln. 9-10). The specification also states "the similarity of HEMA1 polypeptides to these previously described chemokines demonstrates that the HEMA1 nucleic acids, polypeptides, antibodies and related compounds of the invention may be used to treat, prevent or diagnose a variety of hematopoietic disorders, *e.g.* anemia, leukemia and other cancers" (pg. 9, ln. 22-25). The specification further teaches that expression of SEQ ID NO: 1, in a test cell population is compared to a reference cell population, and that any reference cell population can be used, as long as the hematopoietic status of the cells in the reference population is known. However, the specification does not teach any method steps or examples (i.e. experiments with patients showing a correlation with the claimed methods and a disease such as leukemia, for example) of assessing hematopoietic status, diagnosing the susceptibility to a hematopoietic disorder, or of assessing the efficacy of a treatment of a hematopoietic disorder in a subject. The specification also does not disclose which specific cells are used for the test and reference cell populations and how to isolate them from the subject (i.e. applicants' simply state that any cell can be used for the reference cell population, pg. 16., ln. 24-25). In addition, the specification does not disclose how to measure SEQ ID NO: 1 from cells, or how to

determine its normal levels, especially in hematopoietic cells. Furthermore, the specification does not disclose what determines "hematopoietic status". The specification generally states that "hematopoietic status" is meant that is known whether the reference cell has the ability to modulate differentiation and/or proliferation. Therefore, the disclosure does not adequately describe what is really being measured, cell proliferation or differentiation. The specification does not further teach how one of ordinary skill in the art can diagnose or determine the susceptibility to a hematopoietic disorder or assess the efficacy of a treatment of a hematopoietic disorder in a subject. It is not clear what steps are involved in determining this susceptibility or efficacy (i.e. is HEMA1 increased or decreased?).

The prior art of Rossi et al. (J. Immunol. (May 1, 1999) 5490-5497) clearly states that the instantly claimed SEQ ID NO: 1 is expressed by lung bronchoepithelial cells, but does not suggest any relationship of this nucleic acid and hematopoietic status. Rossi et al. teaches Lungkine, a novel CXC Chemokine, which is specifically expressed by lung Bronchoepithelial cell, and corresponds to applicants' SEQ ID NO: 1. Rossi teaches that although this chemokine clusters with other ELR-CXC chemokines, none of them can confidently be assigned to be its human homologue based on sequence identity (see abstract). Rossi also teaches that Lungkine could not be detected in any of the 70 cDNA libraries analyzed corresponding to specific murine cell populations and tissues, except for in the lung and in fetal lung tissue (see abstract). Rossi further teaches that this chemokine may play a potential role in lung development and in lung-specific neutrophil trafficking (see abstract). Therefore, Rossi teaches that this chemokine is only associated with bronchoepithelial cells, that the human homologue of this chemokine is not known, and may be involved with lung development and lung-specific neutrophil trafficking.

The specification simply relies on the similarity of other chemokines (which are not disclosed in the specification), as applicants' assert "the similarity of HEMA1 polypeptides to these previously described chemokines demonstrates that the HEMA1 nucleic acids, polypeptides, antibodies and related compounds of the invention may be used to treat, prevent or diagnose a variety of hematopoietic disorders, *e.g.* anemia, leukemia and other cancers" (pg. 9, ln. 22-25). The specification does not provide any evidence that these previously described chemokines have any correlation with hematopoietic status, diagnosing the susceptibility of a hematopoietic disorder, or assessing the efficacy of a treatment of a hematopoietic disorder. Furthermore, it is not as clear as to what "similarity" HEMA1 has with these chemokines. Absent factual evidence, one skilled in the art would have reason to doubt that sequence similarity alone would reasonably support the assertion that the biological activity of the claimed subject matter would be the same as that of the similar sequence. Furthermore, it is unclear whether the similar sequence identified in the prior art has actually been tested for the biological activity or whether this also is an asserted biological activity based upon sequence similarity to yet a different sequence. It would have been well known in the art that sequence similarity does not reliably correlate to structural similarity and that structural similarity does not reliably result in similar or identical biological activities. For example, it would have been well known that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. In the absence of factual evidence characterizing the structural and functional components of the biomolecule, the effects of these changes are largely unpredictable as to which ones will have a significant effect and which ones will be silent mutations having no effect. Several publications document the unpredictability of

the relationship between sequence, structure, and function, although it is acknowledged that certain specific sequences have been found to be conserved in biomolecules having related function following a significant amount of further research. For example Russell et al. teaches that even with the restriction of functional similarity, protein structures can vary significantly (pg. 345) (Journal of Molecular Biology, 244 (3):332-350, 1994). Lazar et al. (1988, Mol. Cell. Biol. 8:1247-1252) teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect, but that a replacement with serine or glutamic acid sharply reduced biological activity (see the abstract). However, this level of factual evidence is absent here.

It is also noted that with respect to claims 7-9, the specification does not disclose how the claimed method is performed using any mammalian subject, such as a human, especially since the human homolog of SEQ ID NO: 1 is not known. With respect to claim 21, while the specification suggests that the claimed nucleic acid can be used in the treatment of disease, the specification does not teach one of ordinary skill in the art the specific diseases that are capable of being treated with SEQ ID NO: I, and methods that are used with those disease treatments. MPEP 2164.01(c) states: "When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that use". In this particular instance, the use of the term "pharmaceutical" suggests a use in the treatment of a disease, but the specification does not provide one of ordinary skill in the art with any evidence that the claimed nucleic acid can be used with a specific disease.

Therefore, in light of the arguments above, the written description is not commensurate in scope with the claims as they are broadly drawn. Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111,

clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". In the instant case, while the specification has defined a nucleic acid sequence and outlined broad method steps of using the claimed nucleic acid sequence, the specification has not provided an adequate written description of and has not conveyed that at the time of filing applicants were in possession of methods of assessing "hematopoietic status", methods of diagnosing the susceptibility to a hematopoietic disorder, or methods of assessing the efficacy of a treatment of a hematopoietic disorder in a subject.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 5-12, 15, and 54-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 5-12, 15, and 54-56 are indefinite over the recitation of "HEMA1-39 and 40" because it is not clear as to what is meant by this recitation, and furthermore, "HEMA" is not defined in the specification, and it is not an art fixed definition.

B) Claims 1, 5-10 are indefinite over the recitation of "hematopoietic status" because it is not clear as to what is encompassed by this recitation. The specification does not provide a clear definition of this recitation.

C) Claims 1, 5-12 and 15 are indefinite over the recitation of "providing" because it is not clear as to how one provides a test cell population. Applicants could amend the claims to recite "isolating".

D) Claims 1, 5-12 and 15 are indefinite over the recitation of "test cell population" and "reference cell population" because it is not clear as to what is meant by this recitation. Furthermore, these recitations are not defined in the specification.

E) Claims 1, 5-10 are indefinite over the recitation of "at least one cell whose hematopoietic status is known" because it is not clear if the test or reference cell population comprises at least one cell whose hematopoietic status is known. Furthermore, it is not clear as how one determines a cell whose hematopoietic status is known.

F) Claims 1, 6-12 and 15 are indefinite because it is not clear how one determines hematopoietic status (or diagnoses the susceptibility to a hematopoietic disorder or assesses the efficacy of a treatment of a hematopoietic disorder) in a subject (i.e. it is not clear whether the expression in the test cell population must greater, less than, or equal to the expression of the reference cell population to indicate hematopoietic status). The claims should be amended to recite a positive method of assessing hematopoietic status in a subject.

G) Claims 54-55 are indefinite because the claims are drawn to products (i.e. a kit and an array), but not recite any components to the product. Applicants could amend the claims to recite, " a kit comprising" or "an array comprising"

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 16-18, 21 and 56 are rejected under 35 U.S.C. 102(a) as being anticipated by Rossi et al. (J. Immunol. (May 1, 1999) 5490-5497).

Rossi teaches GenBank Accession No. AF082859, which is a novel CXC chemokine (termed lungkine), specifically expressed by lung bronchoepithelial cells (pg. 5490 and 5492), and is 100% identical to applicants' SEQ ID NO: 1 (see sequence search). Rossi also teaches the amino acid sequence that is encoded by AF082859 (pg. 54592), which is 100% identical to SEQ ID NO: 2 (the polypeptide encoded by SEQ ID NO: 1). The reference also teaches a vector and host cell comprising the nucleic acid molecule encoding a polypeptide comprising an amino acid sequence that is at least 75% identical to SEQ ID NO: 2. With respect to claim 21, Lungkine is considered to be a composition (i.e. a nucleic acid) comprising the nucleic acid molecule encoding a polypeptide comprising an amino acid sequence that is at least 75% identical to SEQ ID NO: 2. With respect to claim 56, AF082859 comprises SEQ ID NO: 1.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 54 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rossi et al. (J. Immunol. (May 1, 1999) 5490-5497).

Rossi teaches GenBank Accession No. AF082859, which is a novel CXC chemokine

(termed lungkine), specifically expressed by lung bronchoepithelial cells (pg. 5490 and 5492), and is 100% identical to applicants' SEQ ID NO: 1 (see sequence search). Rossi does not teach a kit comprising SEQ ID NO: 1. However, reagent kits were conventional in the field of molecular biology at the time the invention was made. In particular, kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatability of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged SEQ ID NO: 1, in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art.

12. Claims 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rossi et al. (J. Immunol. (May 1, 1999) 5490-5497), in view of Schena (PNAS (1996) 93:10614-10619).

Rossi teaches GenBank Accession No. AF082859, which is a novel CXC chemokine (termed lungkine), specifically expressed by lung bronchoepithelial cells (pg. 5490 and 5492), and is 100% identical to applicants' SEQ ID NO: 1 (see sequence search). Rossi does not teach an array comprising SEQ ID NO: 1.

Schena teaches the advantages of a nucleic acid array comprising a nucleic acid.

"Microarrays offer a number of advantages over other potential high-capacity approaches to expression analysis. The chip-based approach enables small hybridization volumes, high array densities, and the use of fluorescence labeling and detection schemes . These features provide a set of performance specification that are unattainable with filer-based approaches" (pg. 10618).

Schena also teaches that parallel gene analysis with microarrays provides a rapid and efficient method for large-scale human gene discovery (see abstract).

One of ordinary skill in the art would have been motivated to use the nucleic acid of Rossi and the array of Schena in order to have produced an array comprising claimed SEQ ID NO: 1, for the benefit of assaying a large number of samples. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the nucleic acid of Rossi and the array of Schena, to form an array comprising claimed SEQ ID NO: 1, to have provided a more efficient method for large scale gene discovery.

Conclusion

13. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
June 18, 2001

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